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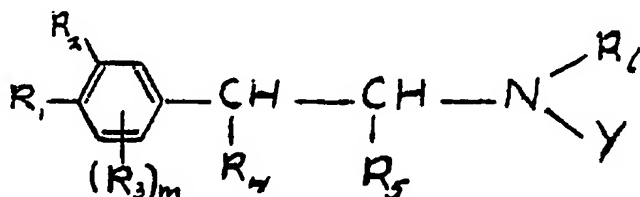
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Tertiary arylethyl amine derivatives having opiate-antagonistic activity.

The invention relates to a group of tertiary arylethyl amine derivatives having opiate-antagonistic activity. The compounds have the general formula 1



(1)

wherein

R_1 is hydrogen, an optionally esterified hydroxyl group or mercapto group, a group $-NHR_3$ or $-CONHR_3$, wherein R_3 is hydrogen, alkyl having 1-8 C-atoms or alkylcarbonyl having 1-7 C-atoms;

R_2 is hydrogen or, when R_1 is hydrogen, one of the other meanings of R_1 , or

R_1 and R_2 together with the 2 carbon atoms of the benzene ring constitute a heterocyclic group which consists of five or six ring atoms and which comprises a group $-NH-$ and, optionally may comprise an oxygen atom, sulphur atom or nitrogen atom as a second hetero atom;

R_3 is hydrogen, alkyl, alkoxy or alkylthio having 1-4 C-atoms, amino, mono- or dialkylamino having 1-4 C-atoms per alkyl group, hydroxyalkyl, alkyl-, alkylamino- or alkoxycarbonyl having 1-4 C-atoms in the alkyl group, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, alkylsulphonyl having 1-4 C-atoms, or aminosulphonyl;

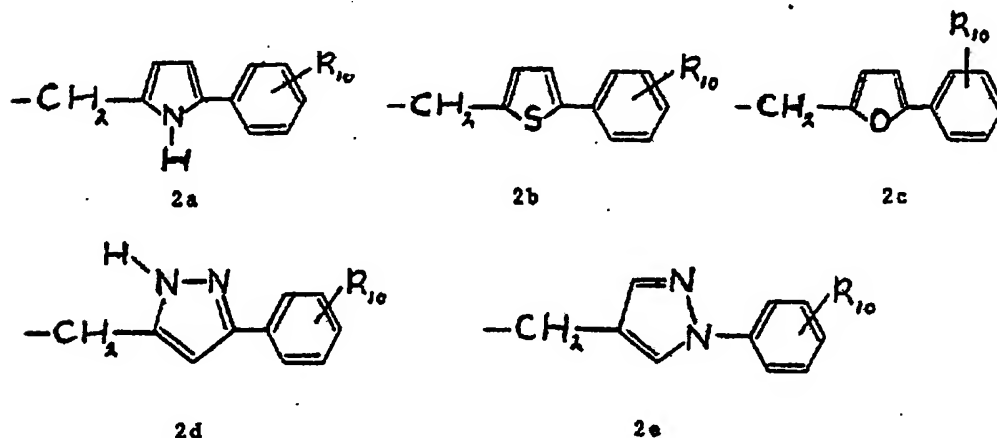
m has the value 1, 2 or 3;

R_4 is hydrogen, alkyl or alkoxy having 1-3 C-atoms, or hydroxyl;

R_5 is hydrogen; alkyl, phenylalkyl, hydroxyalkyl, methoxyalkyl, alkylcarbonyl, alkoxycarbonyl or alkylaminocarbonyl having 1-8 C-atoms in the optionally branched alkyl group;

R_6 is straight or branched alkyl, alkenyl or cycloalkylalkyl or cycloalkyl, having at most 8 C-atoms;

Y is a group R_7-X-R_8 , wherein R_7 is a straight or branched alkylene chain having 3-8 C-atoms with at least 3 C-atoms between the nitrogen atom and group X ; X is the carbonyl group or ketalised carbonyl group, or the group $CHOH$, CHC_6H_5 , CH_2 , $-CONH-$ or $-CO-NCH_3$ or an oxygen atom or sulphur atom; and R_8 is an alkyl group, cycloalkyl group or cycloalkylalkyl group having at most 10 C-atoms a phenyl group or phenylalkyl group having 1-4 C-atoms in the alkyl group, which groups R_8 can be substituted with one or more groups R_3 ; or Y is a group of the formula 2a-2e



wherein R_{10} may have the meanings given for R_3 .

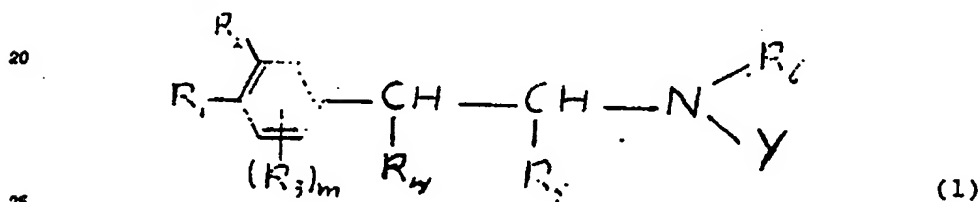
Tertiary arylethyl amine derivatives having opiate-antagonistic activity.

The invention relates to tertiary arylethyl amine derivatives having opiate-antagonistic properties. The invention also relates to the salts and prodrugs of these compounds, to a method of preparing the active compounds, and to pharmaceutical compositions comprising at least one of these new compounds or a salt or prodrug thereof as the active substance.

It is known that in animals and man receptors are present with which endogenous opioids, i.e. opioids which naturally occur in the body, for example the enkephalines, interact. Although the activity of these endogenous opioids can be very favourable in a number of cases, a great number of conditions are known in which the effects of these endogenous opioids are just particularly negative. Compounds which show an antagonistic activity against these endogenous opioids may, therefore be used in the treatment of a number of syndromes in man. Such opiate antagonists may also be used to counteract the effects of exogenous opiates, for example, morphine. For these purposes, substances are preferably used which have a pure opiate-antagonistic effect without an agonistic component in order to avoid the danger of undesired addictive properties associated with opiate-agonism.

A few compounds are known which have a pure opiate-antagonistic activity, notably naloxone, naltrexone and nalmefene. Structurally, these compounds are closely related to each other and to the known exogenous opiate-agonist morphine.

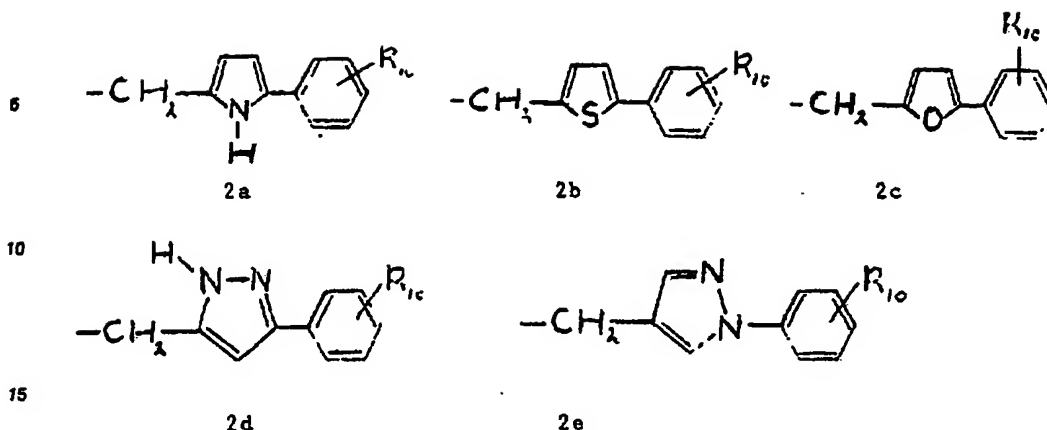
It has now been found that the compounds of the general formula 1:



and the salts thereof have a strong, pure opiate-antagonistic activity.

In formula 1 the symbols have the following meanings:

- R_1 is hydrogen, an optionally esterified hydroxyl group or mercapto group, a group $-\text{NHR}_6$ or $-\text{CONHR}_6$, wherein R_6 is hydrogen, alkyl having 1-6 C-atoms or alkylcarbonyl having 1-7 C-atoms;
- R_2 is hydrogen or, when R_1 is hydrogen, one of the other meanings of R_1 , or
- R_1 and R_2 together with the 2 carbon atoms of the benzene ring constitute a heterocyclic group which consists of five or six ring atoms and which comprises a group $-\text{NH}-$ and, optionally may comprise an oxygen atom, sulphur atom or nitrogen atom as a second hetero atom;
- R_3 is hydrogen, alkyl, alkoxy or alkylthio having 1-4 C-atoms, amino, mono- or dialkylamino having 1-4 C-atoms per alkyl group, hydroxyalkyl, alkyl-, alkylamino- or alkoxycarbonyl having 1-4 C-atoms in the alkyl group, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, alkylsulphonyl having 1-4 C-atoms, or aminosulphonyl;
- m has the value 1, 2 or 3;
- R_4 is hydrogen, alkyl or alkoxy having 1-3 C-atoms, or hydroxyl;
- R_5 is hydrogen; alkyl, phenylalkyl, hydroxyalkyl, methoxyalkyl, alkylcarbonyl, alkoxycarbonyl or alkylaminocarbonyl having 1-6 C-atoms in the optionally branched alkyl group;
- R_6 is straight or branched alkyl, alkenyl or cycloalkyl, having at most 8 C-atoms;
- Y is a group $\text{R}_7-\text{X}-\text{R}_8$, wherein R_7 is a straight or branched alkylene chain having 3-8 C-atoms with at least 3 C-atoms between the nitrogen atom and group X ; X is the carbonyl group or ketalised carbonyl group, or the group $>\text{CHOH}$, $>\text{CHC}_6\text{H}_5$, $>\text{CH}_2$, $-\text{CONH}-$ or $-\text{CO}-\text{N}(\text{CH}_3)_2$ or an oxygen atom or sulphur atom; and
- R_8 is an alkyl group, cycloalkyl group or cycloalkylalkyl group having at most 10 C-atoms a phenyl group or phenylalkyl group having 1-4 C-atoms in the alkyl group, which groups R_8 can be substituted with one or more groups R_3 ; or Y is a group of the formula 2a-2e



wherein R_{1o} may have the meanings given for R_a .

Although some of these compounds (i.e. compounds wherein R_1 or R_2 is hydroxyl) are in the scope of Netherlands patent application no. 7404733 none of the described known compounds has an hydroxylated phenyl group.

The compounds which on the basis of their properties are to be preferred are compounds of formula 1 wherein the symbols have the following meanings, and salts and prodrugs thereof:

R_1 is hydrogen, optionally esterified hydroxyl or aminocarbonyl;

R_2 is hydrogen or, when R_1 is hydrogen, optionally esterified hydroxyl or aminocarbonyl;

R_3 is hydrogen, methyl, methoxy or halogen in the ortho position with respect to the group $-CH(R_4)-CH(R_5)-NR_6Y$;

m has the value 1;

R_4 is hydrogen or hydroxyl;

R_5 is alkyl having 1-3 C-atoms or phenyl ethyl;

R_6 is alkyl having 1-4 C-atoms, propenyl, butenyl or cyclopropylmethyl;

Y is the group R_7-X-R_8 , wherein R_7 is trimethylene, X is carbonyl, >CHOH , $-\text{CONH}-$, $-\text{CH}_2-$ or an oxygen atom, and R_8 is cyclohexyl, phenyl or halogen-substituted phenyl; or Y is a group of formula 2a, 2d or 2e, wherein R_{1o} is hydrogen or halogen.

Compounds according to the invention which are to be preferred in particular are:

- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
- 4-[2-[propyl(4-cyclohexyl-4-oxobutyl)amino]2-methylethyl]benzamide,
- 4-[2-[propyl(4-cyclohexyl-4-hydroxybutyl)amino]-2-methylethyl]benzamide,
- 1-cyclohexyl-4-[propyl[2-(3-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(3-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
- 1-cyclohexyl-4-[propyl[2-(4-benzoyloxyphenyl)-1-methylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-acetoxyphenyl)-1-methylethyl]amino]-1-butanone,
- ammonium 4-[2-[propyl(4-cyclohexyl-4-oxobutyl)amino]2-methylethyl]phenylphosphate,
- N-(4-chlorophenyl) 4-[2-[propyl(4-cyclohexyl-4-oxobutyl)amino]2-methylethyl]phenylcarbamate,
- N-acetyl 4-[2-[propyl(4-cyclohexyl-4-oxobutyl)amino]2-methylethyl]phenylcarbamate,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxy-2-methylphenyl)-1-methylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxy-2-methoxyphenyl)-1-methylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methyl-2-hydroxyethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-ethylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-ethylethyl]amino]-1-butanol,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-propylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-propylethyl]amino]-1-butanol,
- 1-cyclohexyl-4-[propyl[1-(2-phenylethyl)-2-(4-hydroxyphenyl)ethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[methyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
- 1-cyclohexyl-4-[ethyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,

22. 1-cyclohexyl-4-[ethyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
 23. 1-cyclohexyl-4-[butyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
 24. 1-cyclohexyl-4-[2-propenyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
 25. 1-cyclohexyl-4-[2-propenyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
 26. 1-cyclohexyl-4-[3-butenyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
 27. 1-cyclohexyl-4-[3-butenyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
 28. 1-cyclohexyl-4-[cyclopropylmethyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
 29. 1-cyclohexyl-4-[cyclopropylmethyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
 30. 4-[2-[propyl(4-cyclohexylbutyl)amino]-2-methylethyl]phenol,
 31. N-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]butyramide,
 32. 4-[2-[propyl(3-phenoxypropyl)amino]-2-methylethyl]phenol,
 33. 1-phenyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
 34. 1-phenyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanol,
 35. 1-(4-fluorophenyl)-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone,
 36. N-phenyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]butyramide,
 37. 1-cyclohexyl-4-[propyl[2-(5-indolyl)-1-methylethyl]amino]-1-butanone,
 38. 4-[2-[propyl[5-(4-fluorophenyl)pyrrol-2-yl-methyl]amino]-2-methylethyl]phenol,
 39. 4-[2-[propyl[5-phenylpyrazol-3-yl-methyl]amino]-2-methylethyl]phenol,
 40. 4-[2-[propyl[1-(4-chlorophenyl)pyrazol-4-yl-methyl]amino]-2-methylethyl]phenol.

Examples of suitable acids with which the compounds according to the invention can form pharmaceutically acceptable acid addition salts are hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids, for example, citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, benzoic acid, p-toluene sulphonic acid, methane sulphonic acid, naphthalene sulphonic acid, and the like.

Examples of suitable bases with which those compounds according to the invention which comprise an acid group can form pharmaceutically acceptable salts are ammonium hydroxide, sodium hydroxide, potassium hydroxide and calcium hydroxide.

Prodrugs denote derivatives of the compounds of formula 1 which as such are inactive and which, after administration into the body, are converted into an active substance of formula 1.

In those cases in which the group R_4 and/or R_5 in compounds according to formula 1 have a meaning other than hydrogen, the carbon atoms to which R_4 and/or R_5 are bound are chiral centres. In so far as chiral centres are concerned, the invention relates to the various enantiomers of the compound of formula 1 and to the racemates.

On the basis of their opiate-antagonistic activity, compounds according to the invention are extremely suitable for the treatment of those diseases and conditions in man in which endogenous opioids play a part. Examples are: schizophrenia, depression, epilepsy and other diseases associated with the central nervous system, shock, stroke and other disorders associated with the cardiovascular system, ulcers, obesity, respiratory disorders and several types of tumours, especially neuroblastoma. They may also be used for the treatment of patients after an overdose of exogenous opiates, to terminate anaesthesia with exogenous opiates and as an auxiliary agent to prevent recidivism in previous addicts of exogenous opiates.

The compounds according to the invention have been tested for the activities hereinafter in a number of test models. Naloxone was used as a reference substance.

1. Opiate-(ant)agonistic activity *in vitro*.

1.1 Affinity to opiate receptors.

The affinity to (mainly μ -type) opiate receptors was determined by studying the displacement of [3 H]-naloxone in homogenates of rat brains (Pert and Snyder, *Molecular Pharmacology*, **10**, 868-879 (1974)). The results were expressed in K_i -values.

1.2 Opiate-(ant)agonistic activity on the isolated guinea pig ileum and mouse vas deferens.

The opiate-antagonistic activity was determined by studying the antagonism of the effect of the agonists morphine and ethylketazocine on the electrically stimulated guinea pig ileum (μ -type and (substantially) κ -type opiate antagonism, respectively) and the antagonism of the effect of the agonist leucine-enkephaline on the electrically stimulated mouse vas deferens (δ -type opiate antagonism).

The results were expressed in pA_2 values.

In order to establish opiate-agonistic activity, if any, the effect of the test compounds on the electrically stimulated guinea pig ileum and mouse vas deferens was determined. In order to establish whether a found effect, if any, was caused by opiate agonism, the reversal of this effect, if any, by the antagonist naloxone was studied. The above experiments were carried out as described in Magnan et al, Naunyn Schmiedeberg's Arch. Pharmacol. 319, 197-205 (1982), or, for the experiments with ethylketazocine, entirely analogously to the experiments with morphine described in the said publication.

2. Opiate-(ant)agonistic activity in vivo.

Opiate-antagonistic activity in vivo was determined by studying the antagonism of morphine-induced analgesia in mice, measured according to Bianchi and Francheschini, Br. J. Pharmacol. Chemother. 9, 280-284 (1954). Test compounds were administered subcutaneously (sc) or orally (po) in a series of dosages, using five animals for each dose, and the results were expressed in ED_{50} values. In order to establish an opiate-agonistic activity, if any, possible analgetic activity was investigated for the highest dose used in the antagonistic test.

The compounds according to the invention show a structural relationship with the specific muscarinolytics known from the Netherlands Patent Application 7404733. For that reason the affinity to muscarine receptors was determined in addition to that for opiate receptors.

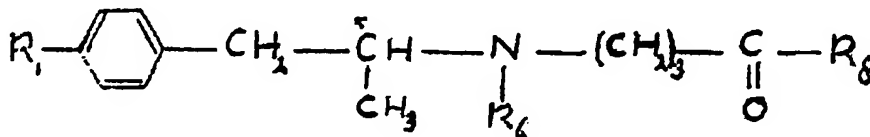
3. Possible anticholinergic side effect in vitro; affinity to cholinergic muscarine receptors.

The affinity to cholinergic muscarine receptors was determined by studying the displacement of [3H] Quinuclidinyl benzilate (QNB) in homogenates of rat brains (Yamamura and Snyder, Proc. Natl. Acad. Sci. U.S.A. 71, 1725 (1974)). The results were expressed in K_i values.

From the tests as described sub 1 and 3 it can be concluded that the structural characteristics which lead to a good opiate-antagonistic and a good muscarinolytic activity, respectively, diverge considerably. This is illustrated in Table 1 with reference to a few compounds. Moreover it must be noted that for the racemic compound b recorded in Table 1, of which the pure R and S isomers were available, the opiate-antagonistic activity was found substantially entirely in the R isomer (c) while the muscarinolytic activity was found substantially exclusively in the S isomer (d).

TABLE 1

Affinity to opiate and cholinergic muscarine receptors of a few compounds from Netherlands Patent Application 7404733 (a to g inclusive), a few compounds of formula 1 according to the present invention (a to d inclusive) and two reference substances.



Comp.	R ₁	R ₆	R ₈	isomer	Affinity to	
					opiate recept. 1)	muscarine receptors 2)
naloxone					1.5	34000
a	hydroxy	propyl	cyclohexyl	rac.	0.8	5.2
b	"	ethyl	"	rac.	25	9.6
c	"	"	"	R	18	450
d	"	"	"	S	200	4.1
e	methoxy	"	n-propyl	rac.	5200	28
f	chloro	"	cyclohexyl	rac.	3750	8.3
g	methoxy	"	"	rac.	1400	2.7
atropine					16200	1.4

1) [³H] naloxone displacement expressed in K_i

2) [³H] QNB displacement expressed in K_i

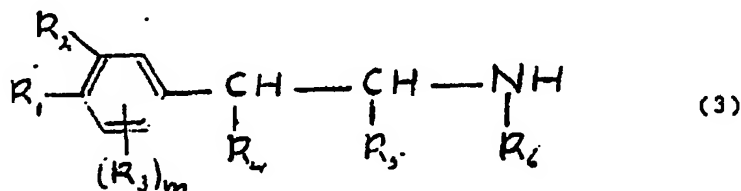
The new compounds according to the invention and the salts and prodrugs thereof can be prepared in a manner known for the synthesis of analogous compounds.

The invention therefore also relates to a method of preparing new tertiary arylethyl amine derivatives of formula 1, wherein the symbols have the meanings given hereinbefore, and the salts and prodrugs thereof.

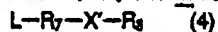
Suitable methods of preparing the compounds of formula 1 as a rule comprise the reaction of a secondary amine of formula 3, or derivatives thereof, with reagents which comprise the group Y, or fragments or derivatives thereof.

Depending on the meanings of the symbols, the compounds of formula 1 can be obtained inter alia by means of any of the following methods.

Compounds of formula 1, wherein Y = R₇-X-R₈, may be obtained, for example, by converting an amine of formula 3



wherein R₁ - R₆ and *m* have the above meanings, with a compound of the general formula 4.



wherein R₇ and R₈ have the above meanings, L is a halogen atom or a tosyloxy group, and X' is a carbonyl group, 1,3-dioxolane group, a >CH-phenyl group or a methylene group, or an oxygen atom or a sulphur atom.

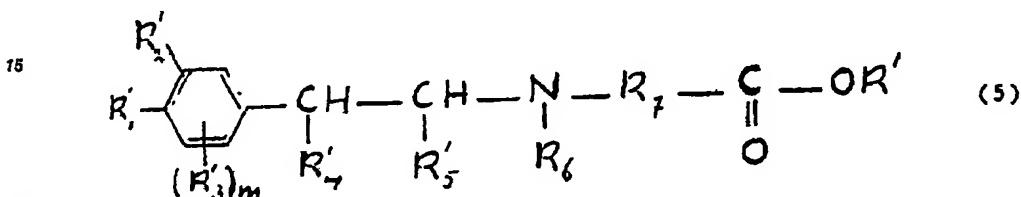
The reaction is preferably carried out in an inert solvent, for example, dimethyl formamide or acetonitrile, or without a solvent, at a temperature of 0-180°C, preferably 20-80°C for 1-48 hours; a base,

for example, triethylamine or sodium carbonate, may be added to the reaction mixture or an excess of the amine (3) may be used; furthermore, in case L is a chlorine atom, NaI may be added to the reaction mixture as a catalyst.

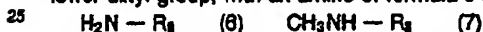
If desired, the resulting compounds of formula 1, wherein $Y = R_7 - X - R_8$ and X is a 1,3-dioxolane group may be converted into the analogous compounds, wherein X is a carbonyl group, by treating with a dilute acid, for example, hydrochloric acid.

The resulting compounds of formula 1, wherein $Y = R_7 - X - R_8$, wherein X is a carbonyl group may then be further converted in known manner (J. Am. Chem. Soc. 93, 2897, (1971)) into analogous compounds, wherein X is a $>CHOH$ group, by treating with a reduction agent, for example, $NaCNBH_4$.

Compounds of formula 1, wherein Y is the group $R_7 - X - R_8$, wherein X is the group $CONH$ or $CONCH_3$, can be obtained by converting an ester of formula 5



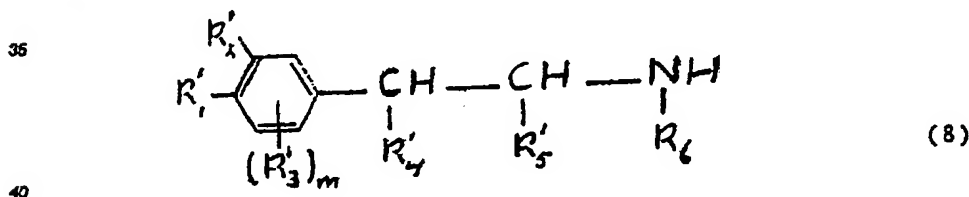
wherein $R'_1 - R'_5$ have the meanings mentioned for $R_1 - R_5$, with the proviso that reactive hydrogen atoms present therein are replaced by a protective group, R_6 , R_7 and m have the above meanings and R' is a lower alkyl group, with an amine of formula 6 or 7



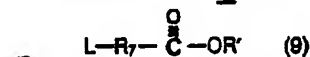
wherein R_8 has the above meaning, and then optionally removing the protective group(s).

The reaction of a compound of formula 5 with an amine (6) or (7) is preferably carried out in a inert solvent, for example, toluene or dimethyl sulphoxide, or without a solvent, in the presence of a base, for example, sodium hydride or sodium methoxide, at a temperature of 0 to 100°C, preferably room temperature, for 1-48 hours.

The esters of formula 5 used as starting substances may be obtained by converting an amine of formula 8



wherein $R'_1 - R'_5$, m and R_6 have the above meanings, with a compound of formula 9



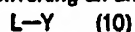
wherein R' , R_7 and L have the above meanings.

The reaction of a compound of formula 8 with a compound of formula 9 is carried out in a manner known for analogous compounds (Patai, "The chemistry of the amino group", pp. 45-55, Interscience Publishers, New York, 1969).

Compounds of formula 1, wherein Y is a group of formulae 2a-2c, can be obtained, for example, by a so-called Mannich reaction. In this reaction the adduct which is formed after treating an amine of formula 3 with formaldehyde, is converted with a 2-phenylpyrrole, 2-phenylthiophene or 2-phenylfuran derivative.

The reaction is carried out in an organic solvent, preferably a protic solvent, and may optionally be accelerated by the addition of an organic or inorganic acid as a catalyst. The reaction temperature is preferably between room temperature and the boiling-point of the solvent used.

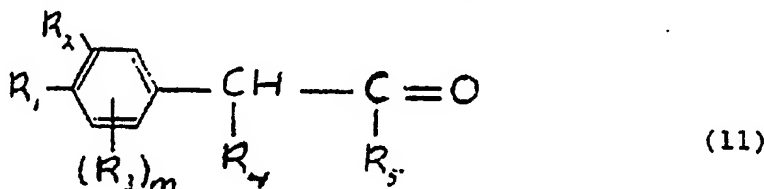
Compounds of formula 1, wherein Y is a group of formula 2d or 2e, can be obtained, for example, by converting an amine of formula 3 with a compound of formula 10



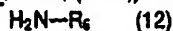
wherein Y is the group 2d or 2e and L is a halogen atom or a tosyloxy group.

The reaction of a compound of formula 3 with a compound of formula 10 is carried out analogously to the above-described reaction of a compound of formula 3 with a compound of formula 4.

The amines of formula 3, wherein R_1 - R_6 and m have the above meanings, used as starting substances can be obtained, for example, by converting a ketone of formula 11

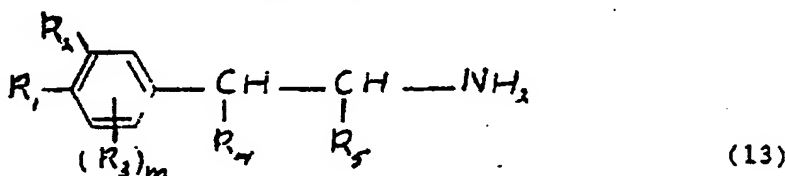


In the presence of a reduction agent in known manner (Org. React. 4, 174 (1948) and J. Am. Chem. Soc. 93, 2897, (1971)) with an amine of formula 12



The ketones of formula 11 are partly known compounds and, as far as they are new compounds, these can be obtained in a manner known for the preparation of analogous ketones.

The amines of formula 3 can further be obtained by monoalkylating an amine of formula 13



In known manner (Patai, "The Chemistry of the amino group", pp. 45-55, Interscience Publishers, New York, 1968), with a compound (14)



wherein L is halogen atom or a tosyloxy group. The amines of formula 3 can also be obtained by converting an amine of formula 13 with a carboxylic acid chloride (see *inter alia* Zabicky, "The chemistry of amides", pp. 73-119, Interscience Publishers, New York, 1956), in such a manner that after reduction with, for example, LiAlH_4 (see *inter alia* Gaylord, "Reduction with complex metal hydrides", pp. 544-594, Interscience Publishers, New York, 1956), the secondary amine (3) is obtained with the desired substituent R_6 .

The amines of formula 13 are partly known compounds and, as far as they are new compounds, these can be obtained in manner known for the preparation of analogous amines.

Within the meanings of R_1 - R_{10} , m , X and Y, a number of chemical conversions known *per se*, for example, reduction reactions, esterifications, amidations, alkylations, dealkylations, etc. may be used as the last step in the reaction to prepare compounds of formula 1.

The invention will be described in greater detail with reference to the ensuing specific examples. The compounds were obtained as a high-boiling-point oil the boiling-point of which could not be determined as a result of decomposition. The compounds were characterized by means of ^1H NMR or ^{13}C NMR.

EXAMPLE I

1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino-1-butanone.

2.92 g (27.5 mmol) of sodium carbonate, 4.13 g (27.5 mmol) of sodium iodide and 6.4 g (27.5 mmol) of 2-(3-chloropropyl)-2-cyclohexyl-1,3-dioxolane were added to a solution of 4.83 g (25 mmol) of propyl[2-(4-hydroxyphenyl)-1-methylethyl]amine in 30 ml of dimethyl formamide and the resulting reaction mixture was stirred for 18 hours at a temperature of 80°C .

After cooling, the reaction mixture was poured on ice and extracted three times with ethyl acetate. After evaporating the organic layer under reduced pressure, the residue was dissolved in a mixture of 30 ml of

dimethyl formamide and 45 ml of 2N hydrochloric acid and stirred for 1 hour so as to split the dioxolane group present. The solution was then extracted three times with diethyl ether, made basic by the addition of concentrated ammonia and extracted three times with ethyl acetate.

The resulting organic layer was washed three times with water and once with concentrated saline, dried on sodium sulphate and evaporated under reduced pressure. The resulting crude product (7.7 g) was purified chromatographically over 200 g of silica gel (Merck, grain size 0.063-0.200 mm) using a mixture of dichloromethane, methanol and concentrated ammonia in the ratio 93:8.5:0.5 as an eluent. After evaporating, 5.5 g (18 mmol) of 1-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]-1-butanone, i.e. the above-mentioned compound 1, were obtained.

The compounds 3, 5, 12, 13, 14, 15, 17, 19, 20, 21, 23, 24, 26, 28, 30, 32, 33, 35 and 37 mentioned hereinbefore were obtained in an analogous manner.

The following derivatives were prepared from the above-mentioned compounds by chemical conversions known per se: 2, 4, 6, 7, 8, 9, 10, 11, 16, 18, 22, 25, 27, 29 and 34.

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EXAMPLE II

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N-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]butyramide.

1.75 g (40 mmol) of sodium hydride (as a 55% dispersion in oil) were added under nitrogen to a mixture of 20 ml of dry dimethyl sulphoxide and 10 ml of dry toluene and stirred at room temperature for 30 minutes. 3.3 g (33 mmol) of cyclohexylamine were added in small portions at 20-25°C while stirring, and the mixture was then stirred at room temperature for 30 minutes. A solution of 8.8 g (30 mmol) of ethyl 4-[propyl[2-(4-methoxyphenyl)-1-methylethyl]amino]butanoate in 20 ml of dry dimethyl sulphoxide and 10 ml of dry toluene was added dropwise and the mixture was stirred at room temperature for 24 hours.

200 ml of water were added to the reaction mixture, the temperature being kept below 30°C.

The aqueous layer was acidified to pH 5 with 2 N hydrochloric acid, then neutralised (till pH 7 to 8) with sodium bicarbonate and extracted three times with diethyl ether.

The aqueous layer was made basic with 2 N sodium hydroxide and extracted three times with methylene chloride.

The collected methylene chloride layers were washed once with little water, dried on sodium sulphate and evaporated under reduced pressure.

The resulting crude product (8.5 g) was purified chromatographically over 250 g of silica gel (Merck, grain size 0.063-0.200 mm) using a mixture of dichloromethane, methanol and concentrated ammonia in the ratio 92.5:7.0:0.5 as an eluent.

After evaporating the collected fractions under reduced pressure, 7.1 g (19 mmol) of pure product were obtained.

The resulting product was dissolved in 140 ml of dichloromethane. At a temperature between -60 and -50°C a solution of 24 g (95 mmol) of borontribromide in 70 ml of dichloromethane were added dropwise under nitrogen in 30 minutes. The reaction mixture was stirred for another 2 hours, the mixture slowly reaching room temperature.

After cooling again to -50°C, 50 ml of H₂O and then 50 ml of concentrated ammonia were added dropwise. After stirring at room temperature for 2 hours, three extractions with dichloromethane were carried out. The collected organic layers were dried on sodium sulphate and evaporated under reduced pressure. The resulting crude product (8.5 g) was purified chromatographically by means of flash chromatography over 600 g of silica gel (Merck, grain size 0.040-0.063 mm) using a mixture of dichloromethane, methanol and concentrated ammonia in the ratio 93:8.5:0.5 as an eluent.

After evaporating the collected fractions under reduced pressure, 3.7 g (10 mmol) of N-cyclohexyl-4-[propyl[2-(4-hydroxyphenyl)-1-methylethyl]amino]butyramide were obtained (compound 31).

Compound 36 was obtained in an analogous manner.

55 EXAMPLE III

4-[2-[propyl(5-(4-fluorophenyl)pyrrol-2-yl-methyl)amino]-2-methylethyl]phenol.

0.8 g (10 mmol) of formalin (content 37%), 1 ml of glacial acetic acid and 1.6 g (10 mmol) of 2-(4-fluorophenyl)pyrrole were added to a solution of 1.9 g (10 mmol) of propyl[2-(4-hydroxyphenyl)-1-methylethyl]amine in 80 ml of absolute ethanol.

After stirring at room temperature for 40 hours, the mixture was neutralised by the addition of concentrated ammonia and evaporated under reduced pressure. Water and dilute ammonia were added to the residue and the whole was extracted three times with ethyl acetate. The collected organic layers were dried on sodium sulphate and evaporated under reduced pressure.

The resulting crude product was purified chromatographically over 200 g of silica gel (Merck, grain size 0.063-0.200 mm) using a mixture of dichloromethane, methanol and concentrated ammonia in the ratio 95.5:4.0:0.5 as an eluent.

After evaporating the collected fractions under reduced pressure, 1.6 g (4 mmol) of 4-[2-[propyl(5-(4-fluorophenyl)pyrrol-2-yl-methyl)amino]-2-methylethyl]phenol were obtained (compound 38).

EXAMPLE IV

4-[2-[propyl(5-phenylpyrazol-3-yl)methylamino]-2-methylethyl]phenol.

1.4 g (16.5 mmol) of sodium carbonate were added to a solution of 1.5 g (7.8 mmol) of propyl[2-(4-hydroxyphenyl)-1-methylethyl]amine and 1.84 g (8.6 mmol) of 3-chloromethyl-5-phenyl-pyrazole hydrochloride in 7.5 ml of dimethyl formamide and the resulting reaction mixture was stirred at a temperature of 70°C for 16 hours.

After cooling, the reaction mixture was poured out on ice and extracted three times with ethyl acetate.

The collected organic layers were washed twice with dilute ammonia, dried on sodium sulphate and evaporated under reduced pressure.

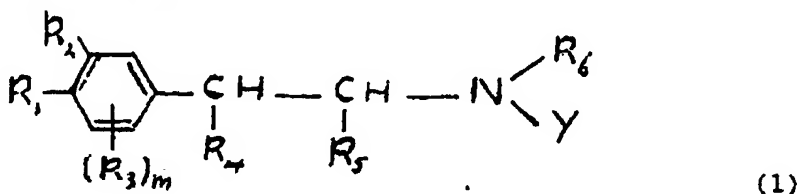
The resulting crude product was purified chromatographically by means of flash chromatography over 300 g of silica gel (Merck, grain size 0.040-0.063 mm) using a mixture of dichloromethane, methanol and concentrated ammonia in the ratio 95.5:4.0:0.5 as an eluent.

After evaporating the collected fractions under reduced pressure, 2.4 g (6.9 mmol) of 4-[2-[propyl(5-phenylpyrazol-3-yl-methyl)amino]-2-methylethyl]phenol were obtained (compound 39).

Compound 40 was obtained in an analogous manner.

Claims

1. Compounds of formula 1



wherein:

R₁ is hydrogen, an optionally esterified hydroxyl group or mercapto group, a group -NHR₃ or -CONHR₃, wherein R₃ is hydrogen, alkyl having 1-6 C-atoms or alkylcarbonyl having 1-7 C-atoms;

R₂ is hydrogen or, when R₁ is hydrogen, may have one of the other meanings of R₁, or

R₁ and R₂ together with the 2 carbon atoms of the benzene ring constitute a heterocyclic group which consists of five or six ring atoms and which comprises a group -NH- and, optionally may comprise an oxygen atom, sulphur atom or nitrogen atom as a second hetero atom;

R₃ is hydrogen, alkyl, alkoxy or alkylthio having 1-4 C-atoms, amino, mono- or dialkylamino having 1-4 C-

atoms per alkyl group, hydroxyalkyl, alkyl-, alkylamino- or alkoxycarbonyl having 1-4 C-atoms in the alkyl group, nitro, cyano, halogen, trifluoromethyl, trifluoromethoxy, alkylsulphonyl having 1-4 C-atoms, or aminosulphonyl;

m has the value 1, 2 or 3;

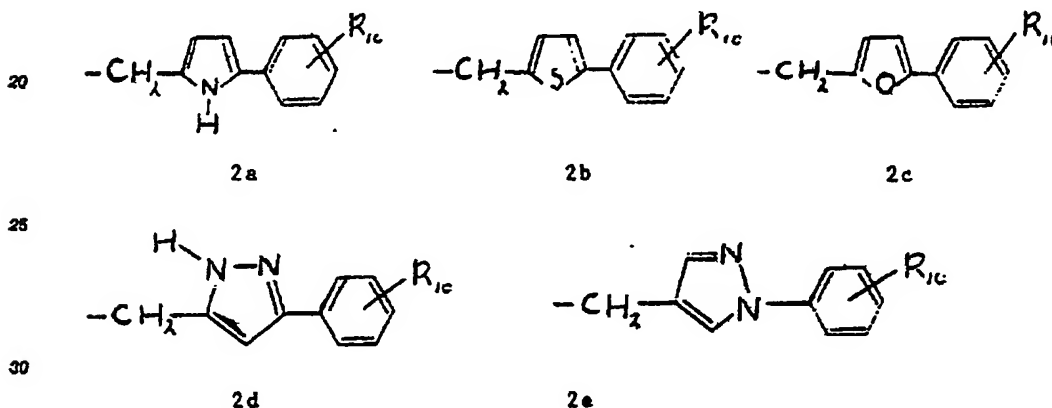
5 R_4 is hydrogen, alkyl or alkoxy having 1-3 C-atoms, or hydroxyl;

R_5 is hydrogen; alkyl, phenylalkyl, hydroxyalkyl, methoxyalkyl, alkylcarbonyl, alkoxycarbonyl or alkylaminocarbonyl having 1-6 C-atoms in the optionally branched alkyl group;

R_6 is straight or branched alkyl, alkenyl or cycloalkylalkyl or cycloalkyl, having at most 8 C-atoms;

10 Y is a group R_7-X-R_8 , wherein R_7 is a straight or branched alkylene chain having 3-8 C-atoms with at least 3 C-atoms between the nitrogen atom and group X; X is the carbonyl group or ketallised carbonyl group, or the group $>CHOH$, $>CHC_6H_5$, $>CH_2$, $-CONH-$ or $-CO-N(CH_3)-$ or an oxygen atom or sulphur atom; and R_8 is an alkyl group, cycloalkyl group or cycloalkylalkyl group having at most 10 C-atoms, a phenyl group or phenylalkyl group having 1-4 C-atoms in the alkyl group, which groups R_8 can be substituted with one or more groups R_{10} ; or Y is a group of the formula 2a-2e

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35 wherein R_{10} may have the meanings given for R_8 , prodrugs and salts thereof.

2. Compounds as claimed in Claim 1 of the formula 1, wherein

R_1 is hydrogen, optionally esterified hydroxyl or aminocarbonyl;

R_2 is hydrogen, or, when R_1 is hydrogen, optionally esterified hydroxyl or aminocarbonyl;

40 R_3 is hydrogen, methyl, methoxy or halogen in the ortho position with respect to the group $-CHR_4-CHR_5-NR_6Y$;

m has the value 1;

R_4 is hydrogen or hydroxyl;

R_5 is alkyl having 1-3 C-atoms or phenyl ethyl;

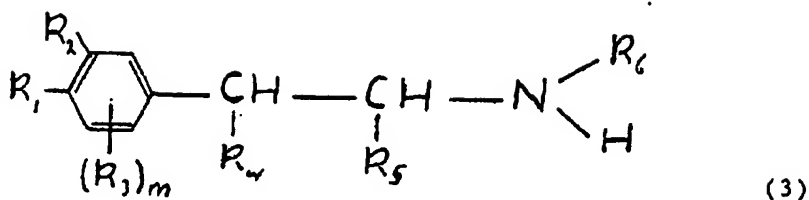
R_6 is alkyl having 1-4 C-atoms, propenyl, butenyl or cyclopropylmethyl;

45 Y is the group R_7-X-R_8 , wherein R_7 is trimethylene, X is carbonyl, $>CHOH$, $-CONH-$, $-CH_2-$ or an oxygen atom, and R_8 is cyclohexyl, phenyl or halogen-substituted phenyl; or Y is a group of formula 2a, 2d or 2e, wherein R_{10} is hydrogen or halogen; and prodrugs and salts thereof.

3. A method of preparing tertiary aryethylamine derivatives, characterized in that compounds as claimed in Claim 1 are prepared in a manner known per se.

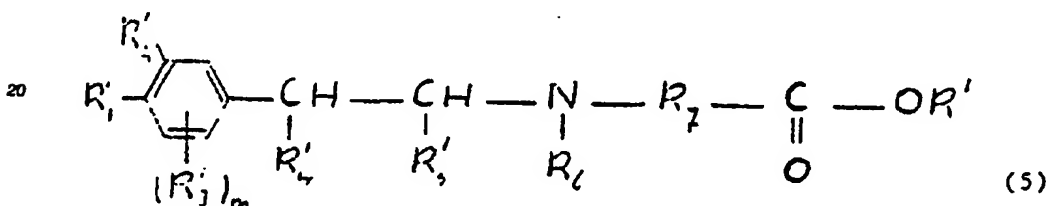
50 4. A method as claimed in Claim 3, characterized in that compounds of formula 1, wherein Y is the group $-R_7-X-R_8$, are prepared by reaction of a compound of formula 3

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10 with a compound of the formula $\text{L} - \text{R}_7 - \text{X} - \text{R}_8$ (4), wherein $\text{R}_1 - \text{R}_8$ and m have the meanings mentioned in Claim 1, L is a halogen atom or a tosyloxy group and X is carbonyl, 1,3-dioxolane, CH-phenyl, $-\text{CH}_2-$ or an oxygen atom or a sulphur atom.

15 5. A method as claimed in Claim 3, characterized in that compounds of formula 1, wherein Y is the group $-\text{R}_7 - \text{X} - \text{R}_8$, wherein X is the group $-\text{CONH}-$ or $-\text{CO}-\text{N}(\text{CH}_3)-$, are prepared by reaction of an ester of the formula 5



25 with an amine of the formula 6 or 7



30 in which formulae $\text{R}'_1 - \text{R}'_6$ have the meanings mentioned in Claim 1 for $\text{R}_1 - \text{R}_6$, with the proviso that reactive hydrogen atoms present therein are replaced by a protective group, $\text{R}_8 - \text{R}_8$ and m have the meanings mentioned in Claim 1, and the protective group(s) are then removed in a manner known per se.

8. A method as claimed in claim 3, characterized in that compounds of formula 1, wherein Y is a group of the formula 2a, 2b or 2c, are prepared by means of a Mannich reaction of an amine of formula 3, formaldehyde and a 2-phenylpyrrole or 2-phenylthiophene or 2-phenylfuran derivative.

35 7. A method as claimed in Claim 3, characterized in that compounds of formula 1, wherein Y is a group of formula 2d or 2e, are prepared by converting a compound of formula 3 with a compound of formula $\text{L}-\text{Y}$ (10), wherein L is a halogen atom or a tosyloxy group and Y is a group of the formula 2d or 2e.

8. A method as claimed in Claim 3, characterized in that a compound of formula 1 is prepared by converting one or more of the groups $\text{R}_1 - \text{R}_{10}$, X and Y in a resulting compound of formula 1 into another group $\text{R}_1 - \text{R}_{10}$, X and Y with the meanings mentioned in Claim 1.

40 9. Pharmaceutical composition which comprise at least one compound as claimed in Claim 1 as the active substance.

10. A method of preparing pharmaceutical compositions having opiate-antagonistic activity, characterized in that a compound as claimed in Claim 1 is brought into a form suitable for administration.



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EUROPEAN SEARCH REPORT

Application Number

EP 88 20 0648

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Y	GB-A- 586 645 (WELLCOME) * Claims; page 7 *	1,9,10	C 07 C 91/30 C 07 C 97/00
X	GB-A- 587 244 (WELLCOME) * Claims; page 5 *	1,9,10	C 07 C 103/50 C 07 D 207/335 C 07 D 231/12
X	NL-A-8 300 392 (DUPHAR) * Claims *	1,9,10	A 61 K 31/135 A 61 K 31/16 A 61 K 31/40
X	EP-A-0 100 569 (DUPHAR) * Claims *	1,9,10	A 61 K 31/415
Y	EP-A-0 211 254 (DEGUSSA) * Claims *	1,9,10	
Y	US-A-4 337 207 (M. GOODMAN) * Claims *	1,9,10	
X	FR-A-1 477 040 (DEGUSSA) * Claims; page 1 *	1,9,10	
X	FR-A-2 266 495 (PHILIPS) * Claims *	1,9,10	TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
X	FR-A-2 007 623 (DEGUSSA) * Claims *	1,9,10	C 07 C 91/00 C 07 C 97/00 C 07 C 103/00 C 07 D 201/00 C 07 D 231/00 A 61 K 31/00
X	US-A-4 097 500 (S.S. PELOSI, Jr.) * Claims *	1,9,10	
D,X	GB-A-1 500 434 (PHILIPS) * Claims *	1,9,10	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 22-07-1988	Examiner MOREAU J.M.
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